

REMARKS/ARGUMENTS

The Status of the Claims.

Claims 61 to 82 are pending with entry of this amendment. Claims 67, 68, 70, 75 to 77, and 79 to 81 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 67, the amendment merely corrects a typographical error, as suggested by the Examiner, with Applicant's appreciation. Claims 68 and 70 include corrections to spelling errors.

With respect to claims 75, 77, 79, and 81, support for the high resolution parameters can be found throughout the specification. For example, see specification at page 26 and in the Appendices.

Applicants submit that no new matter has been added to the application by way of the above Amendments. Accordingly, entry of the Amendment is respectfully requested.

The Drawings.

The Office has requested insertion of SEQ ID NOs for the sequences of Figure 3. Applicants have submitted a new Figure 3A identifying each line of sequence presented as Figure 3 with the appropriate SEQ ID NO.

Compliance with the Sequence Listing Rules.

Applicants have previously submitted a sequence listing for this case in the Preliminary Amendment of August 31, 2004. Applicants believe the present listing covers all sequences of the application requiring formal sequence listing.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on 1/11/05 and 4/25/06.

The Office has requested hard copies of references listed in Appendix I of the original specification. Applicants note that copies of these references have been previously provided and are a matter of record in the family of related cases and can be copied from the files of parent applications, e.g., from the file of application 08/764,870, now U.S. patent 6,236,946.

Objections to the Specification.

The Title has been objected to for allegedly failing to be descriptive of the claims. Applicants appreciate the suggested Title and have amended the specification herein to adjust the Title accordingly.

Applicants appreciate identification of a typographical error in the remarks of Appendix 8. Applicants have amended Appendix 8 to confirm the identification throughout the rest of the specification that the ligand is a GC-1 ligand.

35 U.S.C. §112, Second Paragraph.

Claim 75 to 82 were rejected under 35 U.S.C. §112, second paragraph, as for alleged indefiniteness of the term "high resolution".

Applicants have amended claims 75, 77, 79 and 81 to further clarify the resolution of the claims is from 2 to 3 angstroms. Further, the phrase has been deleted as unnecessary to claims 76 and 80. Because the parameter is no longer specified in relative terms, Applicants request withdrawal of the rejection.

35 U.S.C. §112, First Paragraph.

Written Description of the Claims is Adequate. Claims 61 to 82 were rejected under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the written description requirement. Applicants traverse.

The “written description” requirement has been formulated in a number of different ways over the years. One relatively clear current concise statement of the written description requirement set forth by the courts is as follows:

The [written description] requirement may be satisfied if claim terms ‘readily convey distinguishing information concerning their identity, such that one of ordinary skill in the art could visualize or recognize the identity of a member of the genus.’ *Amgen Inc. v. Hoescht Marion Roussel, Inc.* 65 USPQ2d 1385 (Fed. Cir. 2003).

The Action argues that the pending claims fail to meet the written description requirement because the specification does not provide “sufficient description of a representative number of species by actual reduction to practice, ... drawings ... or by disclosure of relevant, identifying characteristics ... sufficient to show applicant was in possession of the claimed genus.”

Applicants respectfully disagree with both the analysis and the Action’s conclusions, because the specification, in fact, provides an extensive teaching with respect to the structural and functional characteristics of the claimed genus, providing a thorough teaching of the claimed genus, including many specific working examples, thus providing one of skill art in this mature field with tremendous available information regarding the nature of the claimed genus. In fact, the specification provides a tremendous wealth of information that easily enables one of skill to “recognize the identity of a member of the genus,” as required to meet the written description requirement.

It will be appreciated that “The written description inquiry is a factual one and must be assessed on a case-by-case basis.” *Crown Operations International, Ltd.* And *Marshall H. Krone v. Solutia, Inc.*, 62 USPQ2d 1917, at 1922 (Fed. Cir. 2002) citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) (quoting *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (“Precisely how close the original description must come to comply with the description requirement of § 112 must be determined on a case-by-case basis.”)). As is shown below, the present case

easily meets the written description requirement and, indeed, provides far more information than one of skill requires to "recognize the identity of a member of the genus," as the written description requirement requires.

Applicants note that the present claims are to methods, not to products potentially discoverable using the methods. The claims are clearly not "reach through" claims. The *Eli Lilly* case is not on point here because the claims are to methods with consistent steps, not to compositions having a variety of undisclosed related sequences.

Applicants note that, even based on statements of the Office, written description must be adequate, particularly for claims generally limited to embodiments reduced to practice. In items 9 and 10 of the Action, the contributions of the specification are acknowledged, yet all the claims, including dependent claims limited, e.g., to thyroid receptor embodiments and/or modeling based on the provided structural information of the Appendices, are inappropriately rejected as not adequately described. Further, independent claims 75, 77, 79 and 81 are essentially restatements of methods expressly provided in the text of the original specification. Applicants note that a factual basis for the rejection of these claims is not present in the Action. Applicants request the Office at least reconsider the rejections of these independent claims and all dependent claims.

Even with regard to the more generic independent claims 61 and 62, there is a sufficient description of reduction to practice and disclosure of relevant, identifying characteristics sufficient to show Applicant was in possession of the claimed genus and for one of skill to recognize a member of the genus. Although the scope of material input to the methods may be considered broad, the practice of the methods themselves, as claimed, has a narrow range of actual embodiments, well within those provided in the disclosure of the invention. The specification goes well beyond the required description of the narrow method steps of the claims to describe techniques and information more than that required to practice the invention, as claimed. Although not an aspect of the current claims, the specification describes: the range of nuclear hormone receptors (pages 16 et seq), structural and sequence information along with identification of functional modular domains (pages 17 to 22), expression and crystallization methods (pages 22-27), generation of structure data and preparation and use of structural models (pages 27 to 52). Specific examples, with regard to

thyroid hormone nuclear receptors show several examples of success and techniques that can be used with other members of the closely related nuclear hormone super family. One skilled in the art could readily visualize or recognize the identity of a member of the genus, e.g., of a method of providing nuclear hormone receptor structural information and accessing the information.

Because the claims are expressly wholly described in the original specification or well described even beyond the range of methods actually claimed, Applicants respectfully request withdrawal of the rejections for alleged inadequate written description.

The Claims are Enabled. Claims 61 to 82 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Applicants traverse.

As a preliminary matter, according to MPEP 2164.02, a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. The Action acknowledges enablement of a method of using a model of TR having structural coordinates of Appendices 3-8. Therefore, Applicants respectfully request, at the outset, that the enablement rejection be withdrawn with regard to claims 66, 73, 76, 78, 80 and 82.

Applicants note that the present independent methods claims are fairly simple and straight forward methods. They are not claims to unenabled compositions. The claims do not claim, or require experimentation to discover, e.g., all nuclear hormone receptors, all ligands, or all nuclear atomic coordinate data. The claims are not "reach through" claims to products yet to be discovered. However, should one skilled in the art acquire the resources for input to the methods, the methods themselves, as claimed, are readily practiced without undue experimentation. In a fanciful analogy, practicing a claimed method to making sandpaper from moon dust by gluing dust particles to paper is easy to practice without experimentation even if the unclaimed starting materials are difficult or expensive to obtain.

To be an enabling disclosure under § 112, first paragraph, a patent specification must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is

required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *See id.*

Applicants note that although all claims are rejected in the Action, support for the rejections centers almost exclusively on Wands factors associated with the broadest independent method claim 61. Because the allegations and factual bases for the rejections of other claims are sparse, or non-existent, no *prima facie* case for the rejections of other claims is made and these rejections should be withdrawn.

The breadth of the claims. The Action states that "the claims" are broad, but fails to address the limitations of all but one or two of the claims currently pending. As noted above, the rejection for broadness appears to focus only on independent claim 61 and the broad scope of unclaimed subject matter upon which the invention can be practiced. As described above, even the broadest method claims can be easily practiced upon a broad range of input materials, without undue experimentation. Narrower claims, not discussed in the Action, have often been reduced to practice. The claims do not reach through claims to an as yet discovered invention. The scope is not excessive for claiming unenabled sequences, as in the *Eli Lilly* case. The actual invention, as claimed, is actually quite narrow to particular method steps of accessing and providing information.

The nature of the invention. With regard to the nature of the invention, the Action states the "invention depends on ... identifying some structural feature of the ligands that is 'predicted to result in an altered property.'" Applicants note that the present claims have no such requirement or limitations. The present inventions typically make no predictions as to the properties of ligands or receptors, but only provides methods, e.g., to classify input materials as, e.g., likely to bind or not. It is in the nature of screening methods that there be abundant negative results. Negative results can be as useful as positive results. It is the nature of the invention that the methods are successful in providing useful results in most cases, thus, e.g., the methods of assessing binding interactions are enabled well beyond the standards of the applicable case law and regulations.

State of the art. In the art of screening methods, the Action acknowledges that "using known structural coordinates to study a ligand for designing an altered property is well within the skill level of one in the art." Further, the Action acknowledges that "methods of protein crystallization were well known in the art." The factual argument appears to depend on the difficulty of crystallizing some proteins. However, the present claims are not directed to methods of crystallization, so this line of reasoning is irrelevant to the issue of undue experimentation. Further, as discussed above, the state of the art of obtaining positive and negative results (e.g., evaluating whether or not a given ligand is likely to bind, or not, to a given LBD) is well advanced. Given the method inputs, the methods themselves, as claimed do not require unreasonable experimentation to successfully practice, considering knowledge and reasonable efforts in the art.

Direction provided and working examples. The present specification provides abundant direction and working examples of the invention, as claimed. The examples provided extend across the scope of independent claims and often provide reduction to practice for the inventions as claimed. For example, independent claim 62 is a generic method of using a model, not a claim to a particular model. Given a model to any species of nuclear hormone receptor, for example, the examples provided run the generic range of accessing and modeling to be carried out. With regard to other independent claims, such as, e.g., claims 75, 77, 79 and 81, (for which no case is provided in the Action), the specific direction and examples are present in the specification. The specific directions and examples are only more clear for many dependent claims, for which the bulk of the experimentation has been completed and taught in the specification.

Quantity of experimentation. As discussed above, the quantity of experimentation required for most of the claims is essentially zero, since the methods have already been performed and described in the original specification. Close review of other claims will show that the methods can be carried out with a high degree of success without undue experimentation, as discussed above. For example, determining whether a potential ligand is likely to bind, or not, to a nuclear receptor LBD will succeed more often than not. Keep in mind that even a negative result is a success in the methods. For example, the model

will reject accurately and successfully most "potential" ligands. This can be useful in eliminating test compounds as candidates for further screening or bioassay work.

Relative skill in the art. The skill in the art is high. The artists can easily carry out the methods and evaluate positive and negative results. The artists find screening and evaluation of massive amounts of positive and negative results to be routine.

Because the weight of Wands factors supports a finding of the inventions claimed, Applicants respectfully request withdrawal of the rejections for alleged lack of enablement.

35 U.S.C. § 101.

Claims 76, 78, 80 and 82 were rejected under 35 U.S.C. § 101, as allegedly identical to claims 1, 10, 11 and 22 of parent patent U.S. 6,266,622. Applicants traverse.

Claims 76, 78, 80 and 82 are not identical to claims 1, 10, 11 and 22, respectively. For example, as a dependent claims, claims 76, 78, 80 and 82 include the limitation wherein the structural model employs 2-3Å resolution structural information. Because the cited claims do not include all the limitations of the presently rejected claims, they are not identical and should not be rejected for alleged section 101 double patenting. Therefore, Applicants respectfully request withdrawal of the rejections.

Obviousness Type Double Patenting

Claims 61-75, 77, 79 and 81 were provisionally rejected under the judicially created non-statutory doctrine of obviousness type double patenting based on claims 1-28 of U.S. patent 6,266,622; claims 61-82 were rejected based on claims 1-22 of U.S. patent 6,236,946. Applicants traverse.

The present application is a continuation application (CON) of a divisional application (DIV) of the cited U.S. patent 6,266,622. As such, it is appropriate that the specification of the '622 patent disclose the methods of the present claims, as alleged in the Action. This is a provisional rejection. Should the appropriate situation arise, Applicants may file a terminal disclaimer at the issuance of claims in the present case.

The present application is a continuation application (CON) of a divisional application (DIV) of a continuation in part (CIP) application that issued as the cited U.S.

patent 6,236,946. New subject matter in the CIP application included, e.g., specific high resolution atomic structural data provided in the Appendices. The claims issued in the '946 case include the following:

1. A method of designing a nuclear receptor synthetic ligand comprising:
 - 1) generating a three dimensional model of a protein comprising a nuclear receptor ligand binding domain (LBD) with a bound ligand utilizing data from FIGS. 28, 29, 30, or 31 and a computer programmed for generating said model from said data;
 - 2) determining at least one interacting amino acid of said nuclear receptor LBD that interacts with at least one first chemical moiety of said bound ligand in said three dimensional model;
 - 3) selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety;
 - 4) measuring the reduction or enhancement of the interaction between said interacting amino acid and said second chemical moiety compared to the interaction between said interacting amino acid and said first chemical moiety;
 - 5) generating a designed nuclear receptor synthetic ligand wherein said first chemical moiety is replaced with said second chemical moiety.

The present rejection depends on the statement that "Figure 28 [of patent '946] ... is identical to instant Appendix 3." This is not the case. The two dimensional graphic representation of the Figures is not identical to the precise data bases of the Appendices and can not render them obvious. This rejection must be withdrawn.

35 U.S.C. §102.

Claims 61, 62, 65, 67, 68, 70, 71, 73 and 74 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Zechel et al. (EMBO Journal 13:1425-33; 1994. Claims 61-65, 67-69 and 71-73 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by McKinney (Environmental Health Perspectives, 82: 323-36, 1989). Applicants traverse.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. That is, in order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983).

Claims are not anticipated by Zechel. During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000); emphasis added. Terms in claims must be interpreted "as they would be understood by one of ordinary skill in

the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification." *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Here, the Office is interpreting terms overly broad both in light of usage in the art and as defined in the present specification.

As a preliminary matter, Applicants note that although the term "ligand" may have a generic meaning, the present claims are typically directed to the narrower subject matter of "nuclear receptor ligands", typically bound to "nuclear receptor ligand binding domains" well known in the art to designate specific functional regions of nuclear receptors.

The present rejections are based on an interpretation that is contradictory to usage in the art and in the present specification. DNA binding to the DNA binding domain (DBD) in Zechel is certifiably not of a ligand to a nuclear hormone receptor ligand binding domain (LBD).

The rejection based on Zechel contradicts established standard usage of terminology in the field. Zechel describes "[h]eterodimers of ... retinoic acid receptor (RAR) bind preferentially to directly repeated elements ... due to the specific heterocooperative interaction of their DNA binding domains (DBDs)". Any quick investigation in the field will show standardized terminology in this well documented field clearly distinguishing DBD/DNA interactions from LBD/Ligand interactions in nuclear hormone receptors. For example, the NIH resource for macromolecular modeling and bioinformatics, the Theoretical and Computational Biophysics Group, describes nuclear hormone receptors as "composed of several domains which are differentially conserved between the various receptors and have different roles: a variable N-terminal region, a conserved DNA binding domain (DBD), a variable hinge region, a conserved ligand binding domain (LBD), and a variable C-terminal region. ... The central DBD is responsible for targeting the receptors to their [nucleic acid] hormone response elements (HRE). ... The LBD participates in ... hormone binding". The claims include aspects of nuclear hormone receptor ligands bound to ligand binding domains. Zechel discusses another aspect of nuclear hormone receptors well known to be different receptor elements with different functions.

The rejection based on Zechel contradicts usage and definitions of the terms provided in the present specification. Starting on page 17 of the original specification, the modular functional domains of nuclear receptors is described in several sections. DNA-binding domains (DBDs) are described in the section starting on page 18. LBDs are described starting on pages 19 to 22. It would be unreasonable to confuse DBDs with LBDs in light of this disclosure.

Independent claim 61 is directed to, e.g., accessing structural information from a model of a nuclear hormone receptor ligand bound to a nuclear hormone receptor. Because ligand binding at a nuclear hormone receptor is clearly not the same as binding of a receptor DBD to a hormone response element DNA sequence, Zechel can not be considered to teach or anticipate the claim.

Independent claim 62 and dependent claim 65 are directed to, e.g., accessing structural information specific to a nuclear hormone ligand binding domain. Because Zechel does not discuss LBDs, as discussed above, it can not anticipate these claims.

Claim 70 is directed to, e.g., aspects of a crystal of nuclear receptor ligand bound to a nuclear hormone receptor. Because Zechel does not discuss nuclear receptor ligands bound to anything, it can not anticipate the claim. Moreover, the present Action fails to state a *prima facie* case for failure to even allege such crystals may be found in Zechel.

Claim 71 is directed to, e.g., a computationally designed ligand. This is not found in Zechel, and no *prima facie* case is made because such design is not alleged in the Action.

Further, because dependent claims include all limitations of the claims upon which they are dependent, none of the dependent claims can be anticipated by Zechel. Because none of the claims are anticipated by Zechel, Applicants respectfully request withdrawal of the rejections.

Claims are not anticipated by McKinney. The rejection based on McKinney is based on the contention that "the specification does not disclose a specific definition for a nuclear hormone receptor or a thyroid receptor, but discloses that a nuclear receptor is a receptor for, e.g., thyroid hormones (see specification column bridging pages 16-17)." Applicants have reviewed this paragraph and can find no disclosure that can reasonably be interpreted as

stated in the Action. The paragraph mentions that the methods of the invention "can be used to design drugs for a variety of nuclear receptors, such as [a long list of well known nuclear receptors]". However, it is not logical, based on this disclosure, to suggest that any protein that binds the same ligand as a nuclear receptor can be considered to be a nuclear receptor. Because this is not a reasonable interpretation of the claim terms, the rejections based on McKinney should be withdrawn.

The Action finds anticipation in the statements of McKinney at pages 327. On the contrary, at page 327, McKinney makes it clear that thyroxin-binding prealbumin (TBPA) is a normal human serum protein, TBPA is not a nuclear protein, and TBPA is not considered a nuclear hormone receptor. For example, McKinney repeatedly talks of "TBPA and the nuclear receptor", as distinct, separate and different entities. In the cited paragraph at page 327, McKinney refers to TBPA as a "serum transport protein", "compared and contrasted" to "a hormone nuclear receptor."

At page 330, McKinney mentions that TBPA may have properties in common or aspects of similarity with at least one thyroid hormone nuclear receptor. However, Applicants do not argue that TBPA does not have certain homology with a nuclear receptor, but that TBPA serum transport protein is objectively itself not a nuclear receptor. The Action claims "TBPA ... is considered to be a nuclear hormone receptor binding pocket." This is not clear from the cited reference, and even if it were true, would not teach the present invention. Although McKinney claims to "have demonstrated that prealbuminlike thyroxine-specific binding sites in rat liver nuclear extracts", this does not teach, e.g., methods of using a model of a nuclear hormone receptor bound to a nuclear hormone receptor ligand. In any case, no amount of discussion will turn a serum protein into a nuclear protein.

Applicants note that because the terms are so well known in the art, they did not bother to include a definition of, e.g., nuclear hormone receptor in the Definitions section of the present specification. However, as discussed above with regard to the Zechel rejection, the terms are quite clear based on well established standard usage in the art and based on reading of the present specification. For example, Theoretical and Computational Biophysics Group defines nuclear hormone receptors as ligand-activated transcription factors that regulate gene expression by interacting with specific DNA sequences upstream of their

target genes. The present specification describes nuclear hormone receptors as, e.g., proteins having a DNA-binding domain and a ligand binding domain (see, e.g., the description of nuclear receptors in the sections spanning pages 16 to 22). Furthermore, even a layman would understand that a protein floating free in the blood stream is not a nuclear protein.

With regard to independent claim 61, McKinney does not teach all limitations because, e.g., he does not teach at least providing structural information corresponding to an atomic coordinate model of a nuclear hormone receptor bound to a nuclear receptor ligand.

With regard to independent claim 62, McKinney does not teach at least, e.g., determining whether a potential nuclear ligand is likely to bind to a nuclear hormone receptor ligand binding domain; nor is this ever actually alleged in the Action. Further, McKinney does not teach, e.g., accessing structural information corresponding to an atomic coordinate model of the nuclear hormone receptor ligand binding domain, accessing structural information corresponding to a ligand, or modeling binding of the potential ligand to the nuclear hormone receptor ligand binding domain, thereby determining whether the potential ligand is likely to bind to the nuclear receptor ligand binding domain. Apparently, McKinney does not teach any limitation of the claim, nor has it been properly alleged in the Action.

With regard to dependent claims 69 and 71, although McKinney apparently studies a compound in a cleft, Applicants have been unable to identify, e.g., a teaching in McKinney wherein a modified ligand is designed by selection for a changed amino acid interaction. Although McKinney appears to observe interactions of various compounds, he does not proactively use of a model to computationally design ligands. Again, because there is not a nuclear hormone receptor, there can not be a ligand designed to interact with a nuclear hormone receptor.

Because dependent claims include all limitations of the claims upon which they are dependent, none of the dependent claims can be anticipated by McKinney. Because none of the claims are anticipated by McKinney, Applicants respectfully request withdrawal of the rejections.

35 U.S.C. §103(a).

Claims 66, 76, 78, 80 and 82 were rejected under 35 U.S.C. §103(a) as allegedly obvious based on McKinney in light of case law (*In re Gulack*, 217 USPQ 401 and *In re Ngai*, 70 USPQ2d 1863). Applicants traverse.

Three requirements must be met to state a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. MPEP § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. MPEP § 2143.01. Third, a reasonable expectation of success is required. MPEP § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. MPEP §2143. That is, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. *In re Geiger*, 815 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As a preliminary matter. Because McKinney does not teach all limitations of the independent claims, neither does it teach all limitations of the associated dependent claims. The addition of the cited case law can not provide any additional teachings, e.g., a method of using a model of a nuclear hormone receptor bound to a nuclear hormone receptor ligand. Because not all limitations are taught, McKinney can not render the claims obvious.

The cited MPEP section, and associated case law, concerns the proposition that an old device (e.g., computer) is not made new and non-obvious by incorporation of a data list. Here, the claims are not to a device, but to methods, so the citation is irrelevant to the present claims and does not support the present rejections. Applicants are not here pursuing claims to an old device.

Assuming for sake of argument that the present claims were to a device using the database, the claims would still be non-obvious. According to the cited MPEP 2106,

"[w]hen functional descriptive material is recorded on some computer-readable medium, it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized." Emphasis added.

Applicants agree that music, literature, art, photographs, and mere arrangements or compilations of facts or data, without any functional interrelationship are not a process, machine, manufacture, or composition of matter, so are not subject matter for patent protection. However, the claims at issue are not "mere compilations of data", but claims to methods functionally incorporating structural data to provide a useful output. In addition, there is a functional relationship between the atomic structure data and other components of the methods. For example, the atomic structural information is used in the processes of the methods to provide models used in modeling ligands that can be identified in a biological assay for thyroxin receptor activity. The specific structural data of the Appendices function to influence the modeling and ultimate selection of agonists or antagonists. It can not be said that the data are non-functional in the methods.

The cited case law further supports the non-obviousness of the present claims. For example, a holding in *In re Ngai* is that a different set of printed instructions for an old art kit does not produce a new kit. At page 1864, the Court makes it clear that the inventor "can claim the new use as a **method**, but he cannot claim the existing product itself." Emphasis added. Here we have methods claims, so *In re Ngai* says the claims are new and non-obvious.

The Court in *In re Gulack* finds printed matter rejections questionable. The controlling facts of *In re Gulack* require that the claims be to a product. The present claims are to methods, so again the case is not controlling. Even if this case were relevant (which it is not), the Court found the combination of the device with the printed matter to be non-obvious. Court found the critical question is whether there exists any new and unobvious functional relationship between the printed matter and substrate." Here, the new atomic coordinate data has been shown to function, as discussed above, in methods using the models of the invention. The functional relationship is new and non-obvious because the data is unarguably new; unobvious because it could not have been realized from any cited art or

combination of art. Because the claims are to methods, they can not be obvious based on McKinney and the cited case law. Even if the claims were to a product, they would be non-obvious based on McKinney because the new and non-obvious data of the Appendices functionally interact in the model in new and non-obvious ways. Therefore the rejections should be withdrawn.

Claims are not obvious based on McKinney alone. Claims 75, 77, 79 and 81 were rejected under 35 U.S.C. 103(a) as being obvious in view of McKinney alone. Applicants traverse.

The following is claim 75:

75. A method for identifying a compound capable of selectively modulating the activity of a thyroid hormone receptor (TR) isoform, said method comprising:

modeling test compounds that fit spatially and preferentially into a TR ligand binding domain (TR LBD) isoform of interest using an atomic structural model of a TR LBD isoform bound to a test compound, wherein said atomic structural model employs 2.0Å to 3.0Å resolution structural information corresponding to an atomic coordinate model of the thyroid hormone receptor, or ligand binding domain thereof, bound to the thyroid hormone receptor ligand,

screening said test compounds in a biological assay for TR isoform activity characterized by binding of a test compound to a TR LBD isoform, and identifying a test compound that selectively modulates the activity of a TR isoform.

The present rejection is premised on McKinney allegedly teaching all of the claims but for "screening compounds in a biological assay for TR isoform activity." However, Applicants note McKinney further fails to teach at least: 1) modeling test compounds, 2) modeling test compounds for fit in a thyroid hormone receptor isoform, 3) using an atomic structural model with a 2.0Å to 3.0Å resolution, 4) screening test compounds, 5) screening in a biological assay for TR isoform activity, and 5) identifying a screened test compound that selectively modulates TR isoform activity. Because not all limitations of the claims are taught by the McKinney reference, it can not be considered to render the present claims obvious.

McKinney discusses observations of T3, T4 and chlorinated aromatic hydrocarbons interacting with thyroxine binding prealbumin (TBPA) serum transport protein. A computer model of molecular binding at the TBPA cleft is said to "permit one to estimate the differential free energies of complex formation for compounds of this type [chlorinated

aromatics]." However, the "obvious to screen" argument in the Action can not provide all the limitations cited above.

McKinney has not modeled test compounds, but only observed interactions with thyroid hormones and known toxins of interest.

Those in the art, and McKinney in particular, do not consider TBPA to be a TR isoform. In the art, proteins are isoforms, e.g., when they have similar sequences and similar activities. Applicants note that the sequence of TBPA is largely different from that of TR isoforms. McKinney notes that TBPA has different activities in binding and transport of thyroid hormones in the circulation as compared to the binding and gene expression control functions of TR isoforms. Furthermore, TBPA is not a TR isoform according to in the present specification. The present specification at page 14, line 20, defines TR isoform as "TR proteins encoded by subtype and variant TR genes. This includes TR- α and TR- β isoforms encoded by different genes (e.g., *thra* and *thrb*) and variants of the same genes (e.g., *thrb1* and *thrb2*)." Because TBPA is not a TR isoform, McKinney can not render obvious modeling test compounds for fit in a thyroid hormone receptor isoform, screening in a biological assay for TR isoform activity, or identifying a screened test compound that selectively modulates TR isoform activity. Therefore the rejections must be withdrawn.

Moreover, McKinney makes it clear that although TBPA models help provide general concepts on the stacking and binding interactions of thyroxine like compounds, TBPA is not a model for TR interactions. A major thesis of the McKinney paper is that the affinities and activities of various serum, cytosolic and nuclear thyroid binding proteins are different. McKinney finds the various locations and different affinities of the different proteins is important to the different physiological effects of thyroid hormones and chlorinated aromatic hydrocarbons (CAHs). Indeed, TBPA, cytosolic receptors and nuclear thyroxine hormone receptors are known to have different selectivities and affinities at their binding sites. Therefore, the McKinney TBPA structural model can not act as a TR LBD atomic structural model. The TBPA model can not render the present methods obvious.

The Action apparently finds a teaching of screening in the observation of McKinney at page 332 that CAHs are "T4 agonist/antagonist rather than T3 agonist/antagonist ..." Further, the Action cites in McKinney "the importance of T3 relative

to T4 in thyroid hormone action is largely attributed to the nuclear thyroid hormone receptor *in vitro* studies." Applicants note that these statements are irrelevant to the notion of screening or bioassays and do not form a basis for one skilled in the art to discover the presently claimed inventions.

The test for an implicit of motivation showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). The teachings of McKinney are that binding of molecules to TBPA is influenced by hydrophobic stacking and polar interactions within the binding cleft. One skilled in the art working on the problem of the claims (e.g., identifying compounds that "selectively modulates the activity of a TR"), would not be motivated by McKinney - who does not use a TR and teaches that TBPA and other thyroid hormone binding proteins have different selectivity and affinity for thyroid hormones and CAHs.

There would not be an expectation of success for one in the art to screen test compounds for selective modulation of TR isoforms using the in the non-TR isoform TBPA system of McKinney.

With regard to claims 79 and 81, the Action has not alleged McKinney renders obvious identification of a compound or TR agonist that selectively modulates a thyroid hormone receptor (TR) compared to other nuclear hormone receptors. Thus, a *prima facie* case has not been made. Applicants note that McKinney teaches binding characteristics to a TBPA, which is not a TR in the art and is not a nuclear hormone receptor. Therefore, McKinney can not teach comparing a TR to other nuclear hormone receptors.

Because McKinney does not teach all limitations, provide motivation or provide an expectation of success, the claims are not rendered obvious. Applicants respectfully request withdrawal of the rejections based on McKinney.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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Respectfully submitted,



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Attachments:

- 1) A petition to extend the period of response for 3 months;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet;
- 4) Replacement Drawing Sheet;
- 5) Annotated Drawing Sheet(s) Showing Changes; and,
- 6) A receipt indication postcard.



1

rTRalpha
hTRalpha
hTRbeta
hRARalpha
hRARGamma
hRXRalpha
hRXRbeta
hPPARalpha
hPPARbeta
hPPARGamma
hVDR
hER
hGR
hPR
hMR
hAR

Seq ID No.1
Seq ID No.2
Seq ID No.3
Seq ID No.4
Seq ID No.5
Seq ID No.6
Seq ID No.7
Seq ID No.8
Seq ID No.9
Seq ID No.10
Seq ID No.11
Seq ID No.12
Seq ID No.13
Seq ID No.14
Seq ID No.15
Seq ID No.16

[illegible]

FIG. 3A

[illegible]

FIG. 3A